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(71) Applicant *(for all designated States except US)*: **WOCKHARDT LIMITED** [IN/IN]; Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051 (IN).

(71) Applicants and
(72) Inventors: **JAWEED MUKARRAM, Siddiqui, Mohammed** [IN/IN]; Wockhardt Ltd., L-1, MIDC, Chikalthana, Auragabad 431 210, Maharashtra (IN). **KHAN, Rashid, Abdul, Rehman** [IN/IN]; Wockhardt Ltd., L-1, MIDC, Chikalthana, Aurangabad 431 210 (IN). **MANE, Avinash, Seshrao** [IN/IN]; Wockhardt Limited, L-1, MIDC, Chikalthana, Aurangabad 431 210 (IN).

(74) Common Representative: **WOCKHARDT LIMITED**; c/o Sesha Ramesh, Bandra-Kurla Complex, Bandra (East), Mumbai 400 051 (IN).

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(54) Title: CEFDINIR POLYMORPHIC FORMS, AND IMIDAZOLE SALT

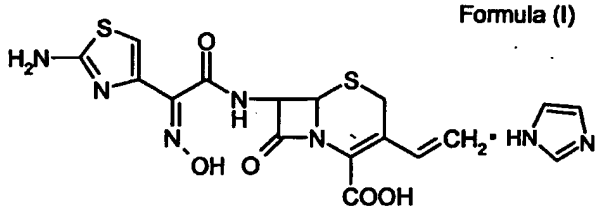
(57) Abstract: A new crystalline Syn-7-[2-(2-amino-4-thiazolyl)-hydroxyiminoacetamido]-3-vinyl-3cephem-4-carboxylic acid-imidazole salt and polymorphic forms C, D and amorphous form of Syn-7-[2-(2-amino-4-thiazolyl)hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid is also disclosed herein.

Cefdinir polymorphic forms, and imidazole salt

FIELD OF THE INVENTION

The present invention relates to a novel crystalline form of *syn*-7-[2-(2-aminothiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (Cefdinir) – imidazole salt having Formula (I)

Formula (I)



Cefdinir-Imidazole salt

which can be used for preparing a cephalosporin antibiotic, e.g., Cefdinir. The said Cefdinir-imidazole salt provides an improved process for isolation of pure, crystalline and amorphous Cefdinir. An efficient process for isolation of Cefdinir in more than 99 % HPLC purity is also discussed herein. Polymorphic crystalline Forms C & D and an amorphous form, their respective preparation methods and characteristics based on specific Infra Red and X-ray powder diffraction values are also discussed in this invention.

BACKGROUND OF THE INVENTION

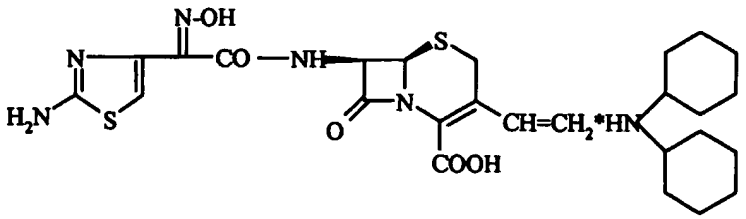
Cefdinir is chemically known as *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid. This molecule was disclosed first time in U.S. Patent No. 4,559,334. It is a third generation Cephalosporin antibiotic and has broader antibacterial spectrum over the general gram positive and gram negative bacteria than other antibiotics for oral administration. It has been reported that Cefdinir has an

excellent antibacterial activity against Staphylococci and Sreptococci. Cefdinir preferably is used in form of monohydrate as antibiotic discussed in J. Antibiotics, Vol. XLI, No. 6, 829 (1988) by Y. Inamoto, et al.

U.S. Patent No. 4,559,334 discloses a manufacturing process of Cefdinir. The process comprises the reaction of 7-amino-3-vinyl-3-cephem-4-carboxylic acid ester with haloacetyloxyacetic acid followed by nitrosation to produce the amino protected ester derivative of Cefdinir. Amino function was made free by treating the intermediate product with thiourea followed by hydrolysis to yield Cefdinir. The patent also discloses Cefdinir sodium salt and ester derivatives of Cefdinir. According to the procedure disclosed in this patent Cefdinir was isolated by chromatographic purification on nonionic adsorption resin followed by pH adjustment to 2.0 with 10 % hydrochloric acid while its sodium salt was isolated by chromatographic purification followed by lyophilization.

Cefdinir may be obtained in impure form according to the known production processes such as disclosed in U.S. Patents 4,559,334; 4,870,168; 6,093,814, WO 92/7840, WO 01/79211, JP 2/000790, JP 4/173781 and JP 1/238587. Since, Cefdinir is synthesized through a complicated reaction consisting of 4 steps from the expensive 7-amino-3-vinyl-3-cephem-4-carboxylic acid derivative impurities increases due to formation of side products or degradation of the molecule and also increases the cost of its production.

PCT application No. WO 98/452299 and U.S. Patent No. 6,350,869 disclose processes for production of crystalline 7-(Z)-[2-(2-aminothiazolyl-4-yl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid / dicyclohexylammonium salt having formula



It is known that Cefdinir is unstable under basic conditions described in J. Pharmaceutical Sciences Vol. 85, No. 9, 976 (1996) and degrades heavily in presence of amines, e.g., *tert*-octylamine under similar conditions. Dicyclohexylamine is a strong base with pKa Value = 10.4 (The Merck Index 13th Edition, Sr. No. 3122, Page No. 545). The yield of Cefdinir dicyclohexylamine salt isolated from crude Cefdinir is not reported in the above reference. The Cefdinir purified by making dicyclohexyl amine salt is isolated in lesser yield due to above discussed factor.

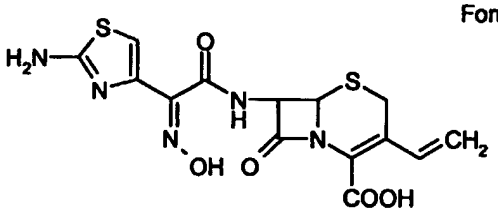
U.S. Patent 4,935,507 and U.S. Patent application 2003/0204082 A1 disclose two different crystalline forms of Cefdinir. The '507 patent claims diffraction angles (°) at about 14.7, 17.8, 21.5. 22.0, 23.4, 24.5 and 28.1 for crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid. The '082 patent application describes a new crystalline form of Cefdinir obtained between a temperature between about 0°C to about +6°C from a dilute aqueous solution of Cefdinir in the presence of at least one organic solvent, in a total percentage (v/v on the aqueous solution) not exceeding 10 % and at a pH between about 1.5 to about 3.0. The X-ray diffraction spectrum of the crystalline Cefdinir obtained in the '082 patent application showed specific d-space values (in angstrom) at about 15.24, 11.30, 10.90, 7.51, 5.66, 5.48, 4.91, 4.76, 4.55, 4.23, 4.17, 3.99, 3.74, 3.64, 3.53, 3.46, 3.39, 3.26, 3.17, 3.08, 2.96, 2.89, 2.82, 2.81, 2.63, 2.57, 2.54, 2.39, 2.31, 1.99 and 1.97.

SUMMARY OF THE INVENTION

The present invention is directed to a new process for the preparation of highly pure crystalline *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (Cefdinir), which has potential applications as anti-microbial agent.

In a first embodiment, the invention is directed to a crystalline Cefdinir-imidazole salt and its manufacturing process from crude Cefdinir having chemical Formula (II)

Formula (II)



Cefdinir

The Cefdinir- imidazole salt is prepared by reacting crude Cefdinir with imidazole in a mixture of acetone and water from about 25°C to about 30°C. In another aspect of the invention, the same salt is produced in a mixture of acetone and methanol by stirring at about 25°C to about 30° C.

According to another embodiment, the present invention is directed to a process for the preparation of crystalline Cefdinir Form C by dissolving Cedinir-imidazole salt in aqueous ethyl acetate and adjusting the pH about 2.5 by sulfuric acid and filtrating the crystals.

In another embodiment, the present invention provides a process for the preparation of crystalline Cefdinir Form D by dissolving Cefdinir-imidazole salt in water at about 55°C followed by adjusting the pH at 2.5 by addition of sulfuric acid and filtering the crystals.

In yet another embodiment, the invention is directed to a process for the preparation of amorphous Cefdinir by dissolving Cedinir-imidazole salt in formic acid and pouring the solution slowly into aqueous methanol.

The Cefdinir-imidazole salt, crystalline Forms C & D and amorphous Cefdinir prepared in the present invention are characterized based on specific Infra Red and X-Ray Powder Diffraction peaks.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an Infra Red Spectrum of crystalline *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid – imidazole salt.

Figure 2 is an X-Ray Diffraction Pattern (XRD) of crystalline *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid – imidazole salt.

Figure 3 is an Infra Red Spectrum of crystalline *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid Form C.

Figure 4 is an X-Ray Diffraction Pattern (XRD) of crystalline *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid Form C.

Figure 5 is an Infra Red Spectrum of crystalline *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid Form D.

Figure 6 is an X-Ray Diffraction Pattern (XRD) of crystalline *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid Form D.

Figure 7 is an Infra Red Spectrum of amorphous *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid.

Figure 8 is an X-Ray Diffraction Pattern (XRD) of amorphous *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid.

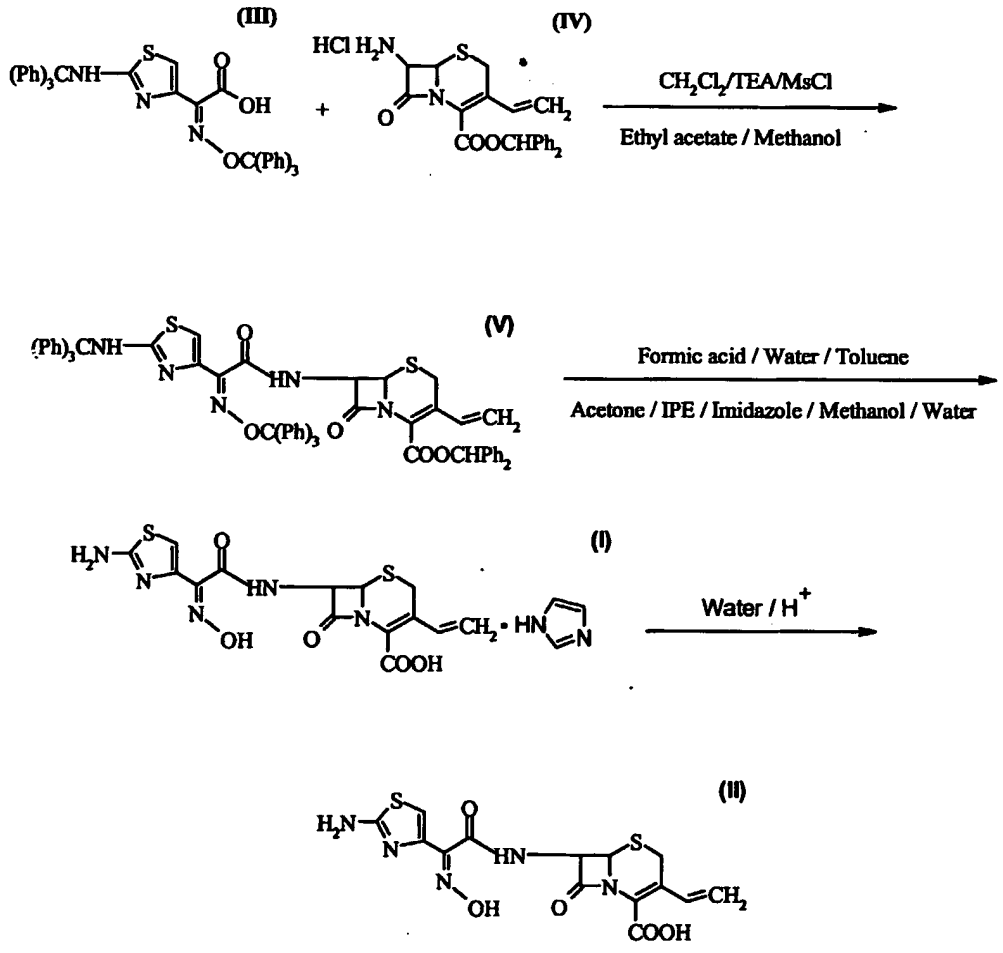
DETALED DESCRIPTION OF THE INVENTION

The present invention relates to a process for the manufacture and efficient isolation process of *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (Cefdinir) by making its imidazole salt and its subsequent hydrolysis in

acidic medium. The preparatory processes of polymorphic Forms C & D and amorphous Cefdinir are also disclosed in aqueous and organic solvents or mixtures thereof.

According to one embodiment, the present invention is directed to a manufacturing process of *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid. The schematic presentation of synthetic process of *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid Formula (II) is shown in Scheme I:

Scheme I



In the present invention, it is observed that impure Cefdinir may be purified by converting Cefdinir into a crystalline salt of Cefdinir with imidazole. Imidazole is a weak

base with pKa Value = 6.92 (The Merck Index, 13th Edition, Sr. No. 4935, Page No. 882) resulting formation of salt without degradation. Cefdinir imidazole salt may be conveniently used to produce highly pure Cefdinir. Moreover, Cefdinir imidazole salt of Formula I is a very useful intermediate in obtaining different new forms of Cefdinir, e.g. Forms C & D and the amorphous form.

A detailed synthetic process of the *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid its imidazole salt and different polymorphic forms are disclosed herein:

(a) Reaction of (Z)-2-(2-Tritylaminothiazol-4-yl)-2-trityloxyimino acetic acid (III) with benzhydril-7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (IV)

(Z)-2-(2-Tritylaminothiazol-4-yl)-2-trityloxyimino acetic acid (III) is treated with methanesulfonyl chloride in dichloromethane using triethylamine as base. The mixture is stirred for one hour at about –10°C and allowed to react further for 1 hour. The temperature used for the reaction is from about –5°C to 0°C. Benzhydril-7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (IV) is reacted with mixed anhydride of 2-(2-tritylaminothiazol-4-yl)-2-(syn)trityloxyimino acetic acid (III) obtained by reaction with methanesulfonyl chloride in dichloromethane to give benzhydril-7-[2(2-tritylaminothiazol-4-yl)-2-(syn)trityloxyimino acetamido]-3-vinyl-3-cephem-4-carboxylate (V) in 80% yield using usual extraction procedure. The reagents used to prepare mixed anhydride of Formula III compound other than methanesulfonyl chloride may be p-toluene sulfonyl chloride, pivaloyl chloride, ethylchloro-formate, isobutyl chloroformate or a complex obtained from dimethylformamide and phosphorous oxychloride, sulfonyl chloride, thionyl chloride or oxalyl chloride in presence of organic base, e.g. triethylamine and tributylamine etc.

(b) Hydrolysis of Benzhydril-7-[(Z)-2-(tritylaminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate

Crystalline compound of Formula V is converted to crude Cefdinir in a single step using 85 to 95 % aqueous formic acid, preferably 90% aqueous formic acid from about 10°C to about 50°C, preferably about 25° to about 35°C. Impure Cefdinir is obtained by concentrating the mixture under vacuum followed by diluting with organic solvent, e.g., acetone, ethyl acetate or di-isopropyl ether etc. or dilution with water. The product is isolated by conventional centrifugation or filtration methods. Crude Cefdinir thus obtained is found in more than 95 % HPLC purity and about 92 to about 95 % yield. Cefdinir in the free form or in the form of a solvate such as hydrate, e.g., monohydrate or in pure form may be obtained from compound of Formula I by dissolving it in water and acidifying the solution with dilute acid to pH from 2.0 to 3.0 preferably between about 2.4 to about 2.8. Precipitated Cefdinir is isolated by conventional filtration or centrifugation techniques.

(c) Preparation of *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid – imidazole salt

According to one embodiment, imidazole salt of *syn*-7-[2-(2-amino-4-thiazolyl)—2-hydroxy-iminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid is obtained by suspending crude *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid in suitable polar solvent. Suitable polar solvents include N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, tetrahydrofuran, alcohols or acetone etc. or combination with water or mixtures of solvents. In particular, suitable solvents include aqueous alcohols, e.g., methanol, ethanol, isopropanol or butanol etc. The preferable ratio of solvent may be methanol or acetone or in combination with water in various ratios, e.g., about 5 : 1, 10 : 1, 20 : 1, 50 : 1, or 100 : 1.This reaction is typically undertaken from about 10°C to about 50°C and more preferably between 15°C to 35°C. Reaction time are typically, between about 1 and about 6 hours, preferably being between about 2 to about 4 hours. The slurry thus obtained is cooled between about 0°C to about 25°C. The crystals obtained using this process are more than 99.5 % pure by HPLC analysis and in 95.5 % isolated yield. Melting point of the title compound is between about 146 to about 148° C. Similarly, in aqueous acetone Cefdinir is formed in more than 99.3 % HPLC purity and in 92.10 % isolated yield.

Characterization of *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole salt

(I) Melting Point

Melting point of the Imidazole salt of *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole salt is observed in the range of 146°C to 148°C.

(II) Infra Red Spectrum

Infra Red spectrum of *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole salt that include peaks at about 3389, 3312, 3155, 2987, 2828, 1768, 1658, 1579, 1533, 1389, 1346, 1173, 1119, 1040, 993, 893, 822, 790, 751 and 630 cm^{-1} (Figure 1).

(III) X-Ray Powder Diffraction

X-Ray Powder Diffraction (2 theta) pattern of *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole salt is characterized that include peaks at about 9.32, 12.42, 13.02, 13.58, 14.68, 15.14, 16.70, 17.74, 18.70, 19.02, 19.52, 20.16, 21.42, 21.46, 21.80, 22.16, 22.56, 23.52, 24.02, 24.38, 25.12, 25.92, 26.14, 26.26, 27.10, 27.64, 28.40, 29.44, 29.74, 30.06, 31.24, 31.50, 31.86, 32.44, 33.94, 34.08, 34.58, 34.96, 36.08 and 38.66° (Figure 2).

(d) Preparation of syn-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid Form C

Syn-7-[2-(2-Amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole salt is dissolved in polar organic solvent, or mixtures of organic solvents or aqueous organic solvents. Suitable polar solvents include, aliphatic esters, more preferably ethyl acetate at a temperature from about 25°C to about 37°C. The organic solvent is preferably taken less than 20 % in water (v/v). pH of the reaction mixture is kept from about 1.0 to about 5.0, more preferably from about 2.0 to about 3.0. Infra Red spectrum of

Syn-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid Form C include peaks at about 3315, 2984, 2361, 1760, 1666, 1613, 1541, 1426, 1353, 1301, 1190, 1136, 1045, 1013, 911, 814, 791, 761, 630 and 570 cm^{-1} (Figure 3). X-Ray Powder Diffraction (2 theta) pattern of *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid Form C that include peaks at about 5.44, 9.18, 10.88, 15.06, 15.50, 17.86, 18.62, 20.72, 20.90, 21.42, 22.340, 23.88, 24.26, 25.68, 26.22, 26.42, 27.80, 28.34, 28.80, 30.46, 32.10, 35.82, 38.60, 38.72 and 39.32° (Figure 4).

(e) Preparation of *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid Form D

According to one embodiment, Crystalline Form D of Cefdinir is obtained by dissolving *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]- 3-vinyl-3-cephem-4-carboxylic acid-imidazole salt in deionized water between about 30°C to 100°C temperature followed by cooling about below 20°C. The preferable pH of the reaction mixture is adjusted between about 2 to about 5.0 more particularly between about 2 to 3.0 for precipitating the title compound. The preferable volume ratio of water in Cefdinir-imidazole salt is between about 20 to 40 times, more particularly about 30 times (v/w). The preferable acid used for pH adjustment is sulfuric acid. Infra Red spectrum of *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid Form D is characterized by the following peaks at about 3304, 2983, 2882, 2361, 1756, 1667, 1610, 1541, 1465, 1423, 1351, 1286, 1189, 1134, 1047, 1014. 992, 813, 651 and 627 cm^{-1} etc (Figure 5). X-Ray Powder Diffraction (2 theta) pattern of *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid Form D is characterized that include peaks at about 8.40, 10.58, 10.70, 10.94, 11.64, 11.74, 11.68, 14.00, 14.22, 14.90, 15.04, 15.24, 15.52, 18.18, 18.76, 19.16, 21.12, 21.26, 21.42, 21.60, 21.90, 22.30, 22.42, 22.66, 23.70, 23.04, 23.94, 24.22, 24.44, 24.52, 24.72, 25.10, 25.36, 25.68, 25.84, 25.98, 26.12, 26.40, 26.65, 27.06, 27.380, 27.520, 27.760, 28.14, 28.54, 28.66, 28.940, 32.10, 36.32 and 39.08° (Figure 6).

(f) Preparation of amorphous *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid

According to one embodiment, amorphous *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid is obtained by dissolving *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]- 3-vinyl-3-cephem-4-carboxylic acid-imidazole salt in organic acid, preferably formic acid or acetic acid. The ratio of Cefdinir -imidazole salt to formic acid is about 1 to 5 times (w/v) preferably 2 times. The acid soluble Cefdinir-imidazole salt is added slowly to the aqueous alcohol between about -20°C to -5°C. The volume ratio of alcohol is preferably below 20 % in water. Infra Red spectrum of amorphous *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid is characterized by the following peaks at about 3306, 2361, 1765, 1634, 1533, 1352, 1167, 1056, 1013, 917, 855, 729, 622, 568 and 490 cm^{-1} (Figure 7). X-Ray Powder Diffraction (2 theta) pattern of the amorphous *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid is shown in Figure 8.

The following examples, illustrate the process of the invention but is by means intended for limiting the scope of the invention.

Examples

EXAMPLE 1

Benzhydril-7-[(Z)-2-(tritylaminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (V).

(Z)-2-(2-Tritylaminothiazol-4-yl)-2-trityloxyimino acetic acid (III, 25.0 gm) is taken in dichloromethane and treated with methanesulfonyl chloride (6.40) in presence of triethylamine base (5.7 gm) at -10°C. The reaction mixture is stirred for 1 hour at -5°C to 0°C and cooled to -10°C followed by treatment with benzhydril-7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (IV, 16.0 gm). The combined reaction mixture is stirred for 2 hours at 0°C. Completion of the reaction is monitored by HPLC. After the said time mixture is poured under stirring into water (250 ml) and layers are separated. Organic

layer concentrated under vacuum and residue stirred with methanol (100 ml). Slurry is stirred for 1 hour and filtered, washed with methanol and dried to obtain 32.0 gm of title compound. Yield : 82.26% and HPLC purity: 98.5 %.

EXAMPLE 2

Crude Syn-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (Cefdinir)

Product (160 gm) obtained from Example 1 is dissolved in 10 % aqueous formic acid (650 ml) and stirred at 30°C for 4 hours. Clear solution is concentrated under vacuum. Residue is diluted with di-isopropyl ether and stirred for 1 hour followed by filtration of the crystals. The crystals are washed with cold di-isopropyl ether and dried to get 56.24 gm of crude Cefdinir. Yield: 93.0 %, HPLC purity: 96.0 %.

EXAMPLE 3

Syn-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid imidazole salt (I). Method 1

Crude *Syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (25.0 gm) as obtained in Example 2 is suspended in methanol (425 ml) and water (25.0 ml) and treated with imidazole (4.5 gm) under stirring. Stirring is continued at 25°C to 30°C for 2 to 3 hours for complete crystallization. Slurry is then cooled to 10°C to 15°C and stirred further for 1 hour. The crystals formed are filtered, washed with cold methanol and dried to obtain 28.0 gm of the title compound. Yield : 95.50%, Melting point:146° to 148°C (decomposition) and HPLC purity: 99.6%.

Method 2

Crude *Syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (25.0 gm) obtained in Example 2 is suspended in a mixture of acetone (125 ml) and water (50 ml). Imidazole (4.5 gm) is added to the solution under stirring at 25 to 30°C. Imidazole salt of Cefdinir crystallizes from solution and is diluted with acetone (750 ml). It is stirred for 1 hour at 25° to 30°C and cooled to 5°C to 8°C and further stirred for 2 hours. The crystals are filtered, washed with cold acetone and dried to obtain 27.0 gm of

titled compound. Yield: 92.10%, Melting point: 146° to 148°C (decomposition) and HPLC purity : 99.4%.

EXAMPLE 4

Pure syn-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (Cefdinir Formula II).

Syn-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole salt (25.0 gm) is dissolved in water (500 ml) between 30°C to 35°C. pH of the solution is lowered to 5.0 by addition of dilute sulfuric acid and charcoal is added. Reaction mixture is stirred for 30 minute at 30° to 35°C and filtered through celite bed. pH of the solution is adjusted to 2.5 to 2.7 between 30° to 35°C. Slurry of the product is cooled to 5°C and stirred for 2 hours for compete crystallization. The crystals are filtered, washed with cold water and dried to obtain 19.20 gm of crystalline Cefdinir. Yield : 90.10% and HPLC purity : 99.5 %.

EXAMPLE 5

Syn-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid Form C

Syn-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole salt (10 gm) is dissolved in 350 ml water, containing 14 % ethyl acetate (v/v) at 30°C. pH of the solution is adjusted to 2.5 by drop wise addition of 10% sulfuric acid (v/v). The same condition is maintained under stirring for 2 hours at 30°C, filtered, washed with deionized water and dried to get title compound. Yield : 94.0 % and HPLC purity : 99.80 %.

EXAMPLE 6

Syn-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid Form D

Syn-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid -imidazole salt (10.0 gm) is dissolved in 300 ml deionized water at 55°C.

The resulting solution is cooled to 30°C and decolorized with carbon (1.0 gm). The solution is cooled to 5°C to 7°C and corrected to pH 2.5 by drop wise addition of 10% sulfuric acid (v/v). It is stirred for 2 hours at the same temperature and left for 14 hours. The crystals of Form D thus obtained is filtered, washed with deionized water and dried. Yield: 90.0 % and HPLC purity : 99.60 %.

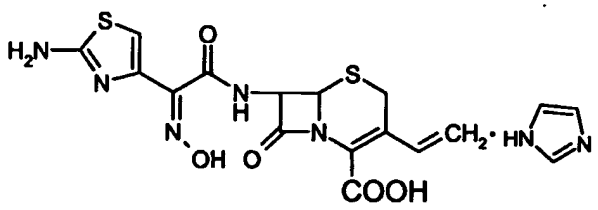
EXAMPLE 7

Syn-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid amorphous

A cold solution of water (200 ml) containing 15 % methanol (v/v) is slowly added to a solution of Cefdinir-imidazole salt (10 gm) taken in 20 ml formic acid at -15°C. After the complete addition the suspension is stirred at the same temperature for 1 hour. Amorphous Cefdinir thus precipitated is filtered, washed with deionized water and dried. Yield: 90.0 % and HPLC purity : 99.10 %.

We Claim:

1 Imidazole salt of Cefdinir having the formula



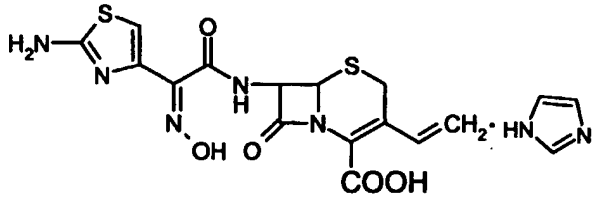
2 The product of claim 1, in substantially crystalline form.

3 The product of claim 1, having a melting point from about 146°C to about 148°C.

4 The product of claim 1, wherein *Syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole salt is characterized by an Infra Red Spectroscopy (IR) spectrum that include peaks at about 3389, 3312, 3155, 2987, 2828, 1768, 1658, 1579, 1533, 1389, 1346, 1173, 1119, 1040, 993, 893, 822, 790, 751 and 630 cm^{-1}.

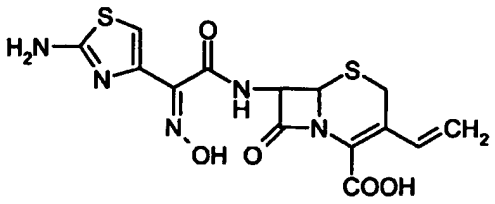
5 The product of claim 1, wherein *Syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole salt is characterized by an X-ray powder diffraction (XRD) that include the peaks at about 9.32, 12.42, 13.02, 13.58, 14.68, 15.14, 16.70, 17.74, 18.70, 19.02, 19.52, 20.16, 21.42, 21.46, 21.80, 22.16, 22.56, 23.52, 24.02, 24.38, 25.12, 25.92, 26.14, 26.26, 27.10, 27.64, 28.40, 29.44, 29.74, 30.06, 31.24, 31.50, 31.86, 32.44, 33.94, 34.08, 34.58, 34.96, 36.08 and 38.66°.

6 A process for the manufacturing a compound of formula



the said method comprising,

(a) subjecting a compound of the formula



with imidazole in a solvent for a sufficient contact time to form *Syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole salt.

(b) isolating the *Syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole salt.

7 The process of claim 6, wherein the molar ratio of *Syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid and imidazole is about 1:1.

8 The process of claim 6, wherein step (a) is carried out in aqueous organic solvent.

9 The process of claim 8, wherein organic solvents are aliphatic alcohols or aliphatic ketones.

10 The process of claim 9, wherein the aliphatic alcohols are methanol, ethanol, 2-propanol or n-butanol and aliphatic ketones are acetone and ethyl methyl ketone.

11 The process of claim 10, wherein more particularly aliphatic alcohol and ketone are methanol and acetone.

12 The process of claim 8-11, wherein the volume ratio of methanol and water is from about 95:5 to about 25:75.

13 The process of claim 12, wherein more particularly methanol and water ratio is 90:10.

14 The process of claim 11, wherein the volume ratio of acetone and water is from about 80:20 to about 40:60.

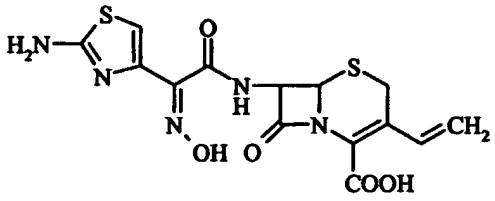
15 The process of claim 14, wherein more particularly acetone and water ratio is 60:40.

16 The process of claim 6, wherein the contacting step is conducted from about 0°C to about 50°C.

17 The process of claim 6, wherein contact time is from about 2 to about 4 hours.

18 The process of claim 6, wherein *Syn*-7-[2-(2-amino-4-thiazolyl) hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole is obtained in more than 99.5 % HPLC purity.

19 A crystalline compound of formula



Form C

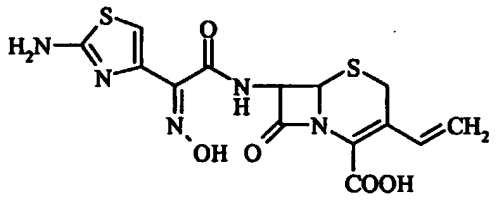
and its pharmaceutically acceptable salts.

20 A pharmaceutical composition comprising compound of claim 19.

21 A product of claim 19, wherein crystalline *Syn*-7-[2-(2-amino-4-thiazolyl) hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole Form C is characterized by an Infra Red Spectrum that include peaks at about 3315, 2984, 2361, 1760, 1666, 1613, 1541, 1426, 1353, 1301, 1190, 1136, 1045, 1013, 911, 814, 791, 761, 630 and 570 cm^{-1}.

22 A product of claim 19, wherein, crystalline *Syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid Form C is characterized by an X-ray powder diffraction (XRD) that include peaks at about 5.44, 9.18, 10.88, 15.06, 15.50, 17.86, 18.62, 20.72, 20.90, 21.42, 22.340, 23.88, 24.26, 25.68, 26.22, 26.42, 27.80, 28.34, 28.80, 30.46, 32.10, 35.82, 38.60, 38.72 and 39.32°.

23 A process for the manufacture of a compound having the formula



Form C

the said method comprising:

(a) contacting *Syn*-7-[2-(2-amino-4-thiazolyl) hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole salt in a solvent or solvent mixture in presence of an acid; and

(b) isolating the *Syn*-7-[2-(2-amino-4-thiazolyl) hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid Form C.

24 The process of claim 23, wherein step (a) is carried out in aqueous organic solvent.

25 The process of claim 24, wherein organic solvent is an ester.

26 The process of claim 25, wherein more preferably ester is ethyl acetate.

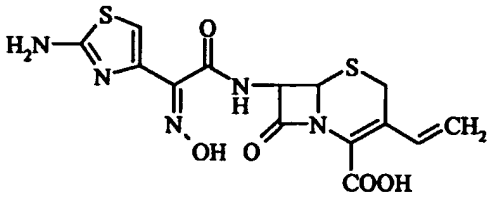
27 The process of claim 23, wherein step (a) is carried out in presence of sulfuric acid.

28 The process of claim 23, wherein pH of the reaction mixture is adjusted from about 1.0 to about 5.0.

29 The process of claim 23, wherein reaction time in step (a) is from about 30 minute to 4 hours.

30 The process of claim 24, wherein organic solvent is less than 20 % in water.

31 A crystalline compound of formula



Form D

and its pharmaceutically acceptable salts.

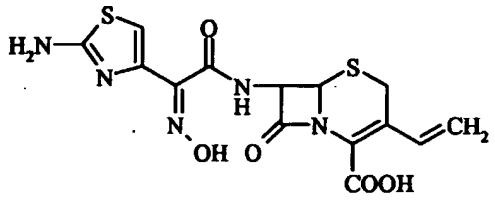
32 A pharmaceutical composition comprising compound of claim 31.

33 The product of claim 31, wherein crystalline *Syn*-7-[2-(2-amino-4-thiazolyl) hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole Form D is characterized by an Infra Red Spectrum that include peaks at about3304, 2983, 2882, 2361, 1756, 1667, 1610, 1541, 1465, 1423, 1351, 1286, 1189, 1134, 1047, 1014. 992, 813, 651 and 627 cm^{-1}.

34 The product of claim 31, wherein crystalline *Syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid Form D is characterized

by an X-ray powder diffraction (XRD), that include peaks at about 8.40, 10.58, 10.70, 10.94, 11.64, 11.74, 11.68, 14.00, 14.22, 14.90, 15.04, 15.24, 15.52, 18.18, 18.76, 19.16, 21.12, 21.26, 21.42, 21.60, 21.90, 22.30, 22.42, 22.66, 23.70, 23.04, 23.94, 24.22, 24.44, 24.52, 24.72, 25.10, 25.36, 25.68, 25.84, 25.98, 26.12, 26.40, 26.65, 27.06, 27.380, 27.520, 27.760, 28.14, 28.54, 28.66, 28.940, 32.10, 36.32 and 39.08°.

35 A process for the manufacture of a compound having the formula



Form D

the said method comprising:

(c) contacting *Syn*-7-[2-(2-amino-4-thiazolyl) hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole salt in a solvent mixture in presence of an acid; and

(d) isolating the *Syn*-7-[2-(2-amino-4-thiazolyl)-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid Form D.

36 The process of claim 35, wherein step (a) is carried out in water.

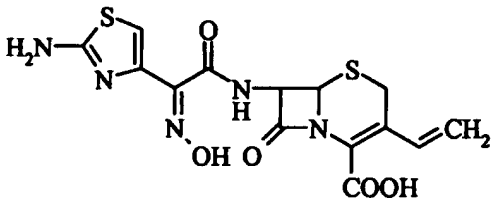
37 The process of claim 35, wherein step (a) is carried out in presence of sulfuric acid.

38 The process of claim 35, where pH of the reaction mixture is between about 2.0 to about 5.0.

39 The process of claim 35, wherein reaction time in step (a) is from about 30 minute to about 4 hours.

40 The process of claim 35, wherein volume of water is about 20 to about 40 times in comparison to *Syn*-7-[2-(2-amino-4-thiazolyl)-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid (v/w).

41 An amorphous compound of formula

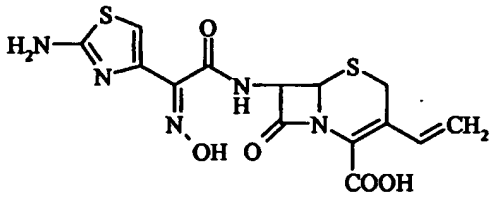


and its pharmaceutically acceptable salts.

42 A pharmaceutical composition comprising compound of claim 41.

43 A product of claim 41, wherein an amorphous *Syn*-7-[2-(2-amino-4-thiazolyl) hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid is characterized by an Infra Red Spectrum, that include the following peaks at about 3306, 2361, 1765, 1634, 1533, 1352, 1167, 1056, 1013, 917, 855, 729, 622, 568 and 490 cm^{-1}.

44 A process for the manufacture of a compound having the formula



Amorphous

the said method comprising:

(a) contacting *Syn*-7-[2-(2-amino-4-thiazolyl) hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid-imidazole salt in a solvent and in presence of an acid; and

(b) isolating the amorphous *Syn*-7-[2-(2-amino-4-thiazolyl)-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid.

45 The process of claim 44, wherein step (a) is carried out in aqueous organic solvent.

46 The process of claim 45, wherein more particularly organic solvent is an aliphatic alcohol.

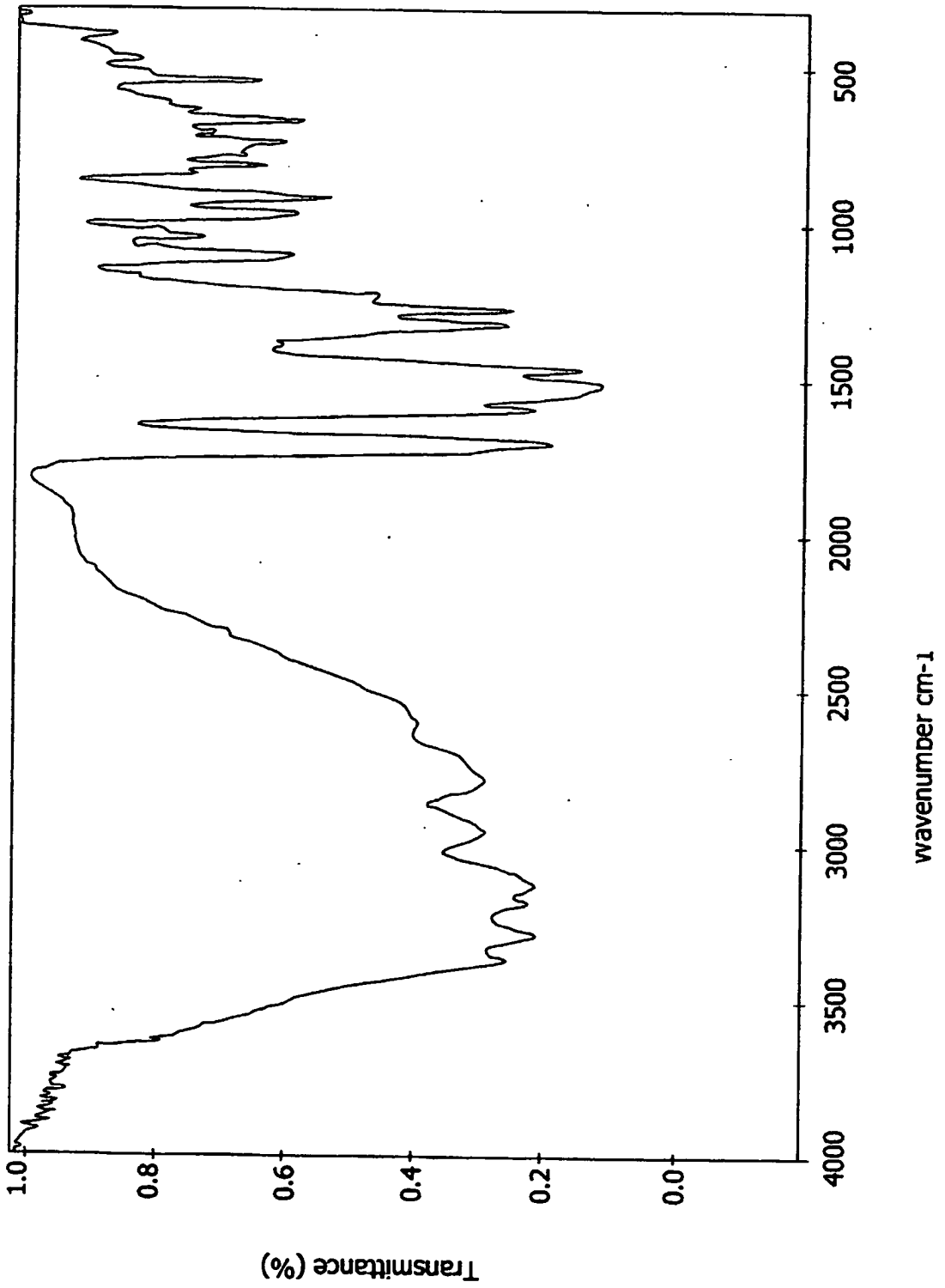
47 The process of claim 46, wherein more preferably alcohol is methanol.

48 The process of claim 44, wherein step (a) is carried out in presence of an organic acid.

49 The process of claim 44, wherein more preferably said acid is formic acid.

50 The process of claim 44, wherein ratio of Cefdinir-imidazole salt and formic acid is about 1:5, more preferably 1:2 (w/v).

51 The process of claim 44, wherein reaction time in step (a) is from about 30 minute to 4 hours.


Transmittance (%)
1.0
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0.6
0.4
0.2
0.0
4000
3500
3000
2500
2000
1500
1000
500
wavenumber cm-1

Figure 1

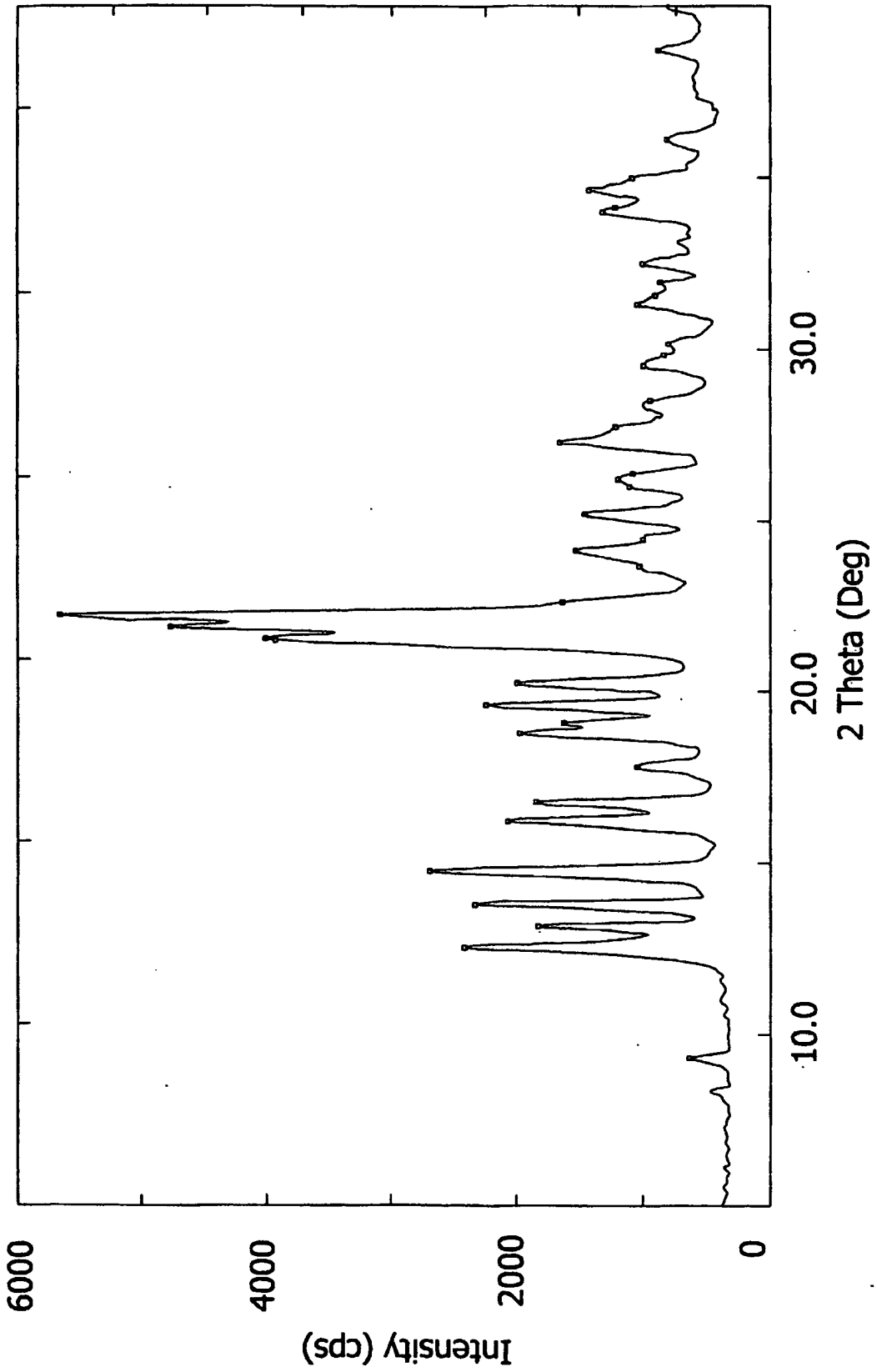


Figure 2

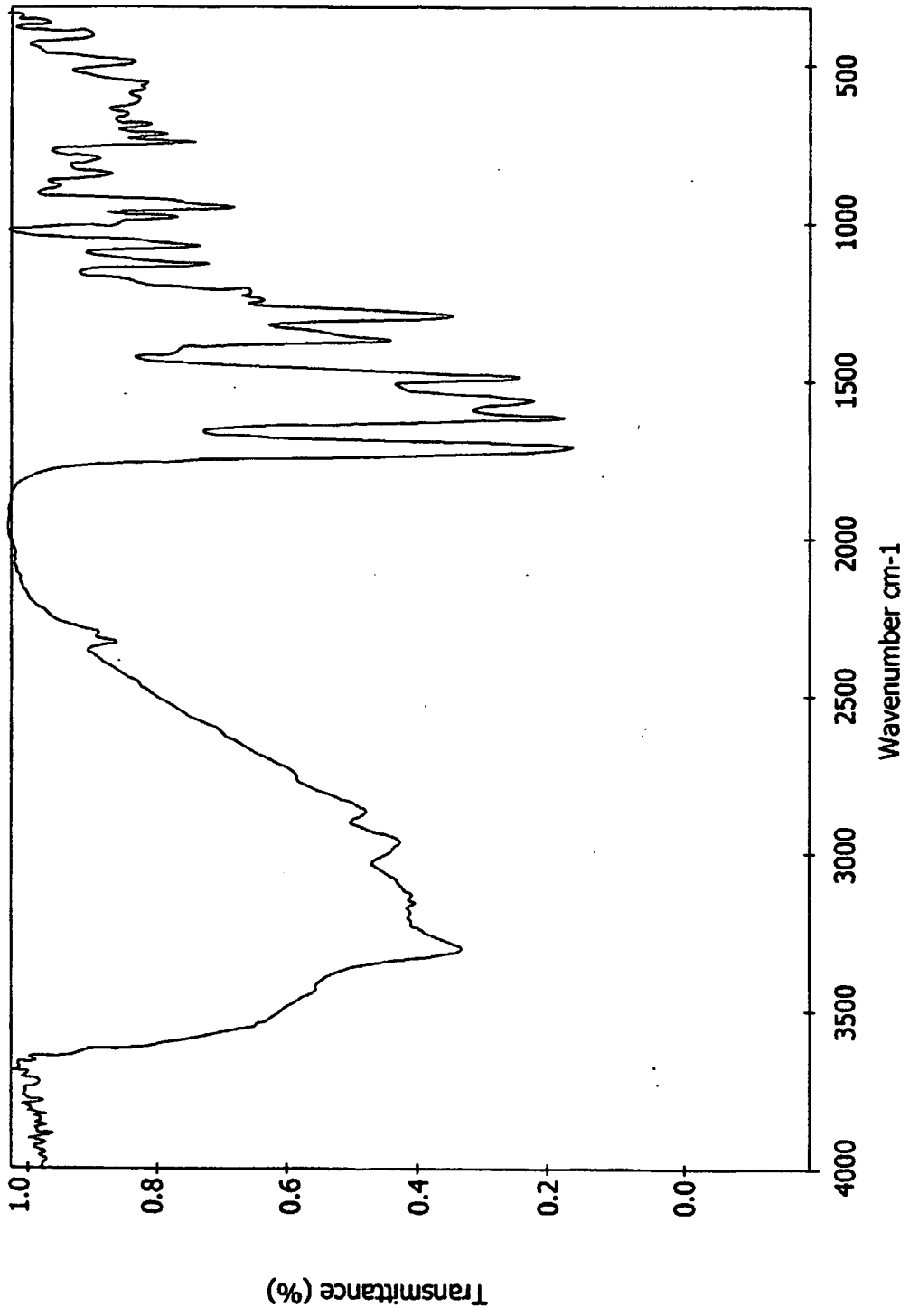
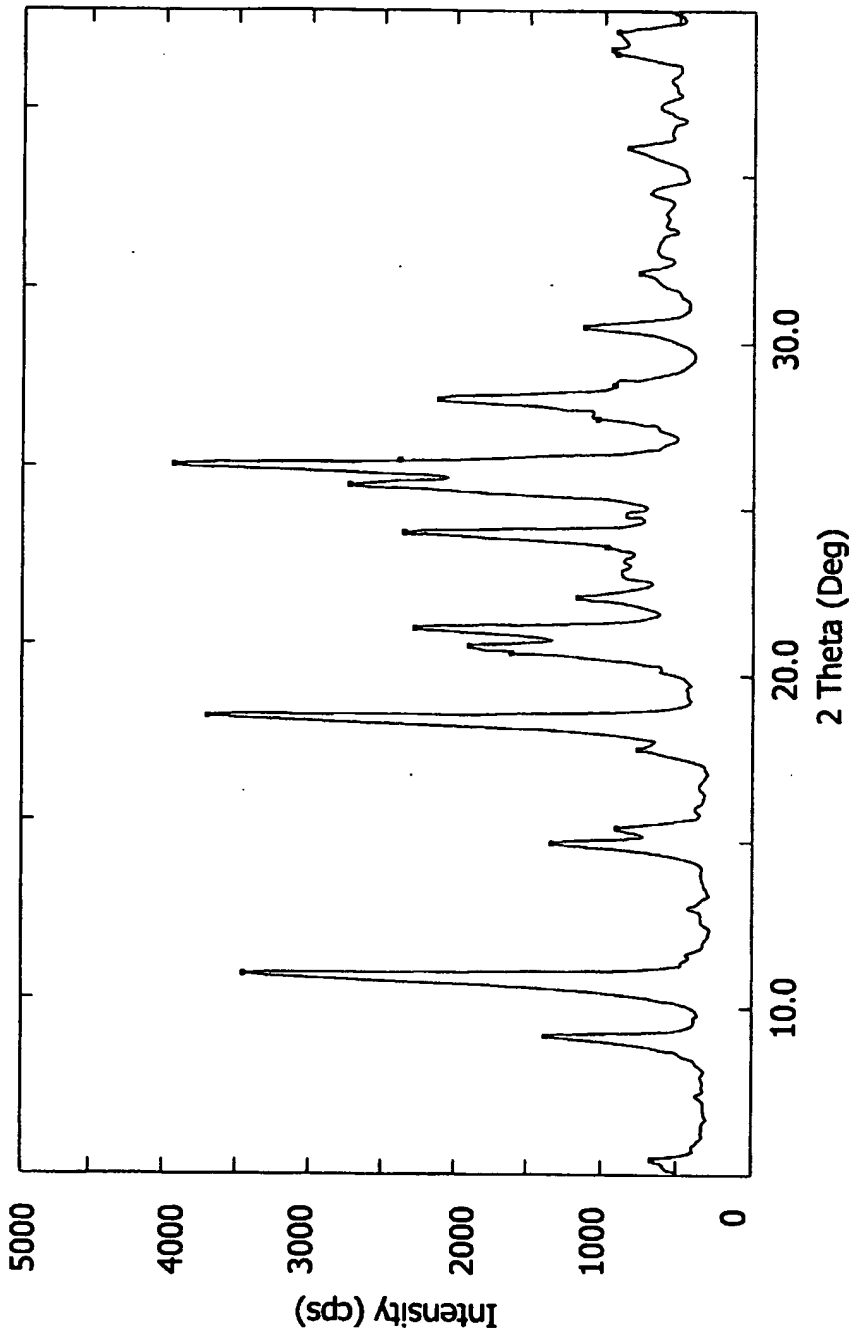

Transmittance (%)
1.0
0.8
0.6
0.4
0.2
0.0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1

Figure 3


Intensity (cps)
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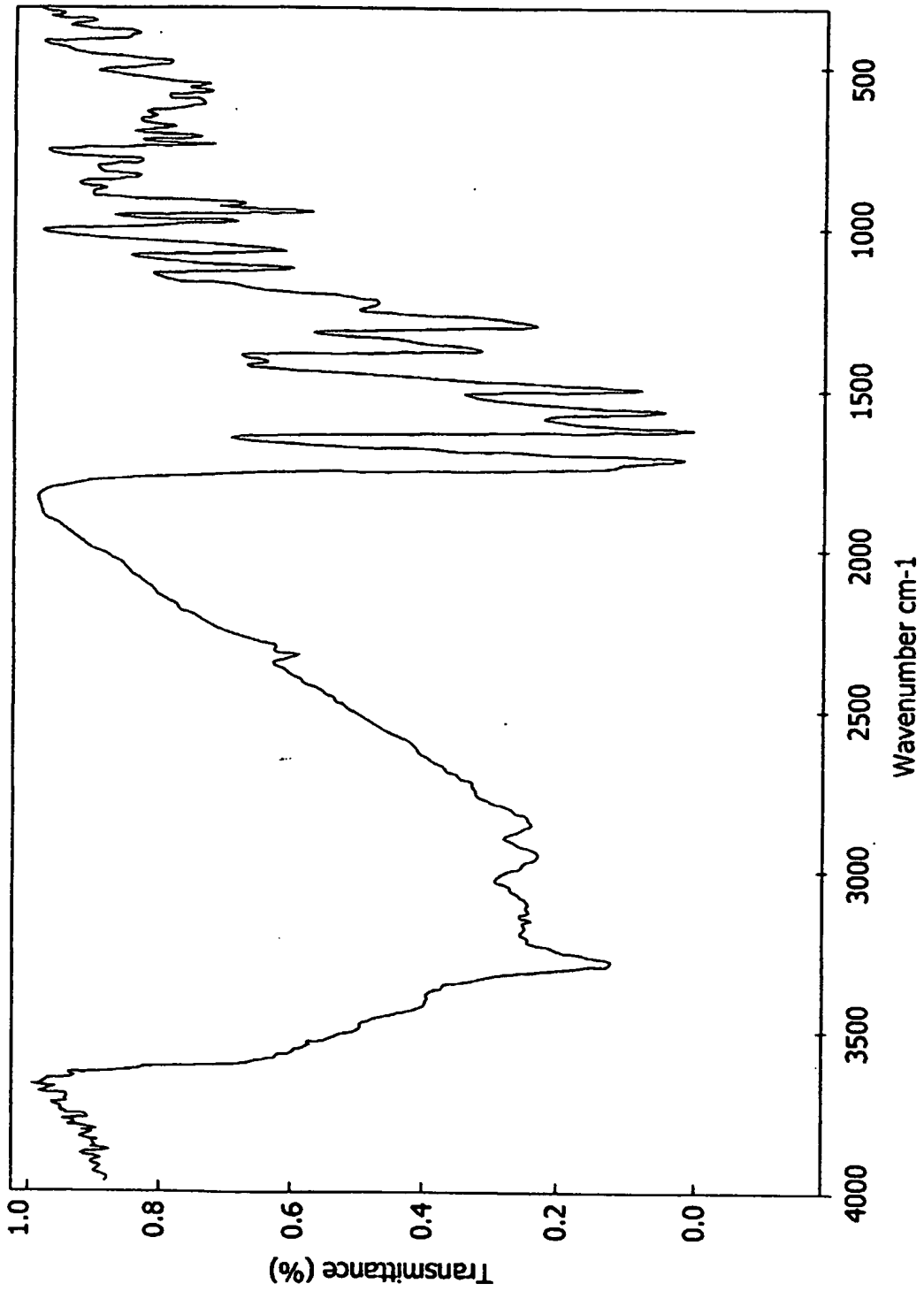
4000
3000
2000
1000
0
10.0
20.0
30.0
2 Theta (Deg)

Figure 4


Transmittance (%)
1.0
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0.6
0.4
0.2
0.0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1

Figure 5

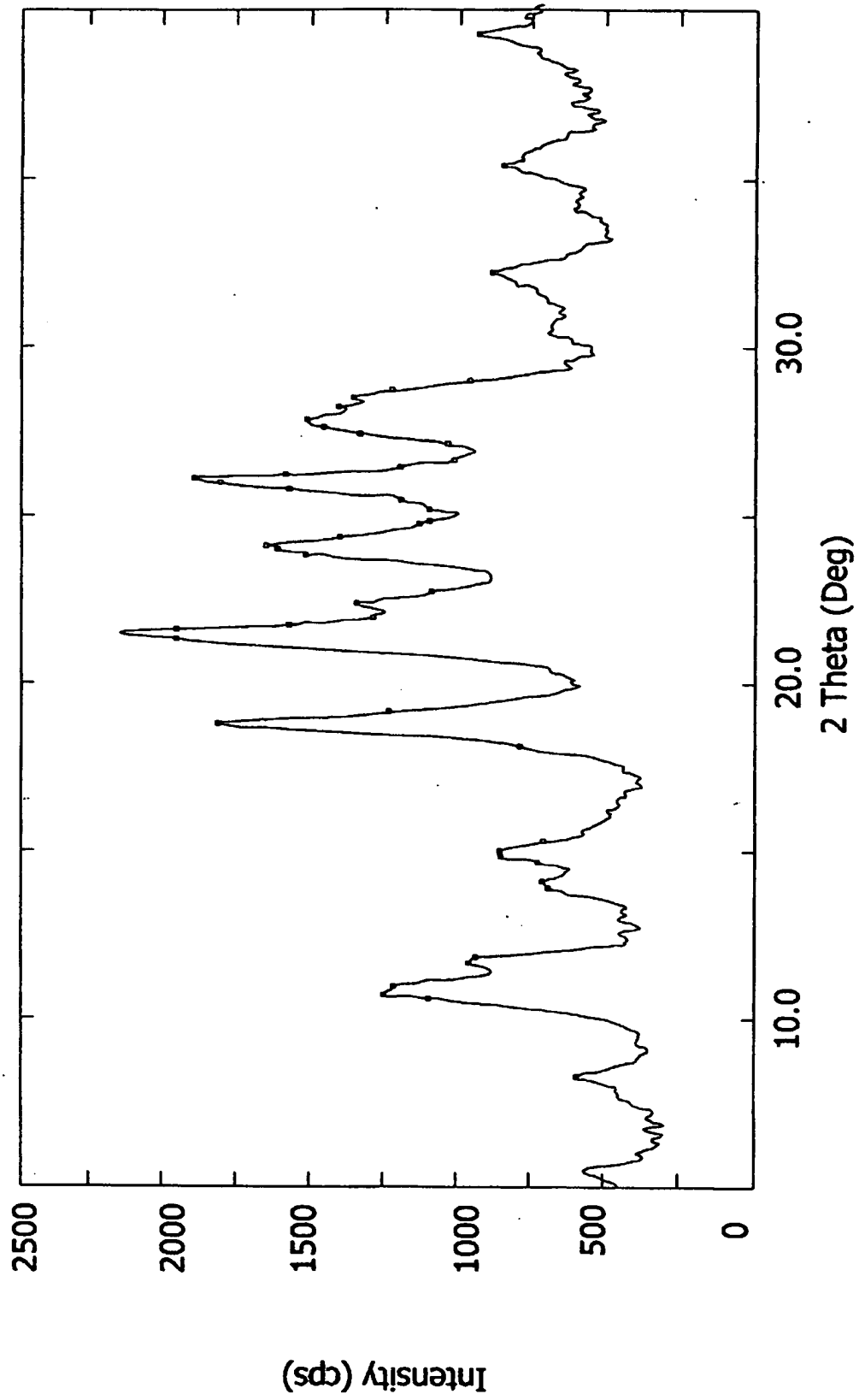
Intensity (cps)
2500
2000
1500
1000
500
0
10.0
20.0
30.0
2 Theta (Deg)

Figure 6

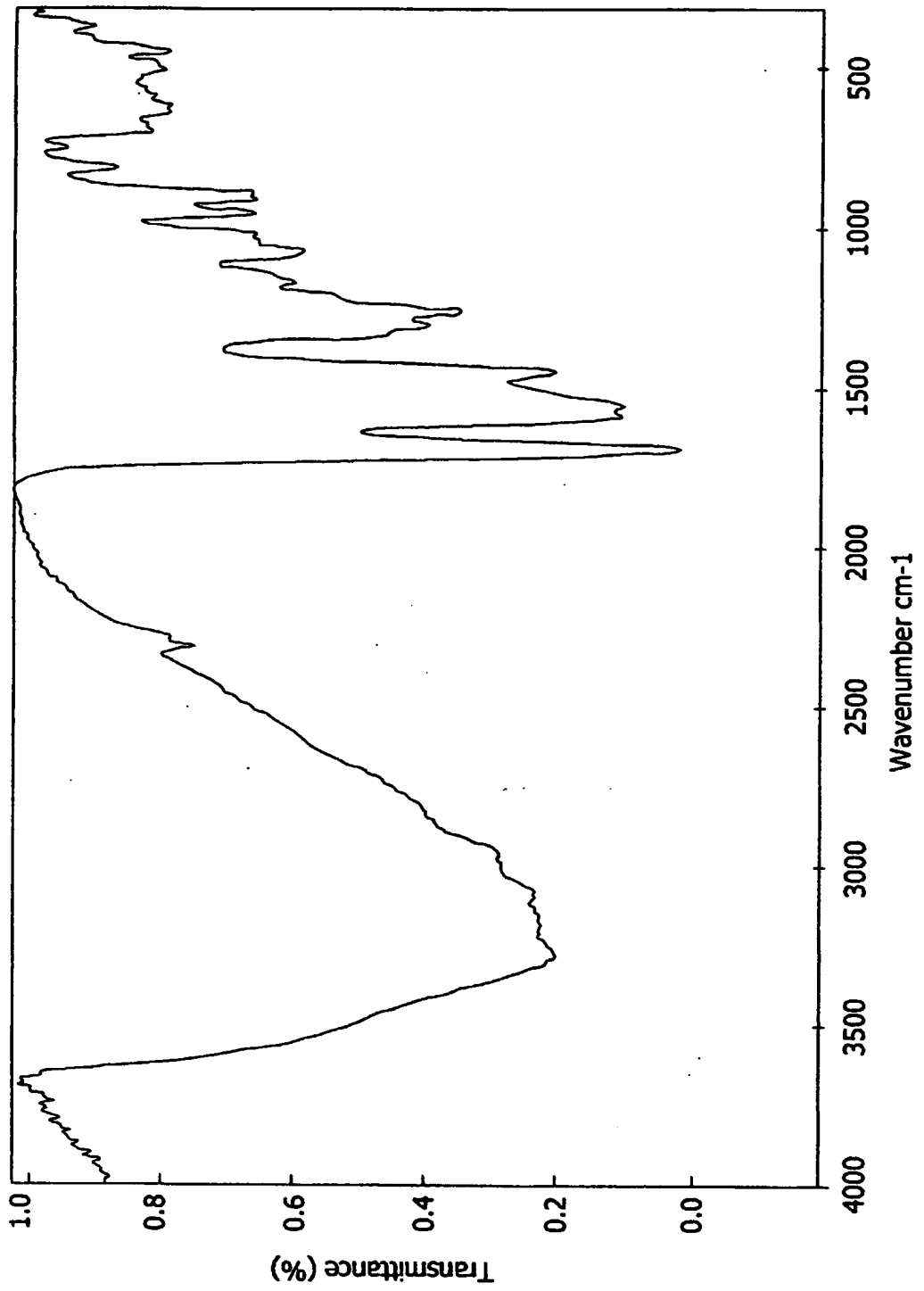
Transmittance (%)
1.0
0.8
0.6
0.4
0.2
0.0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1

Figure 7

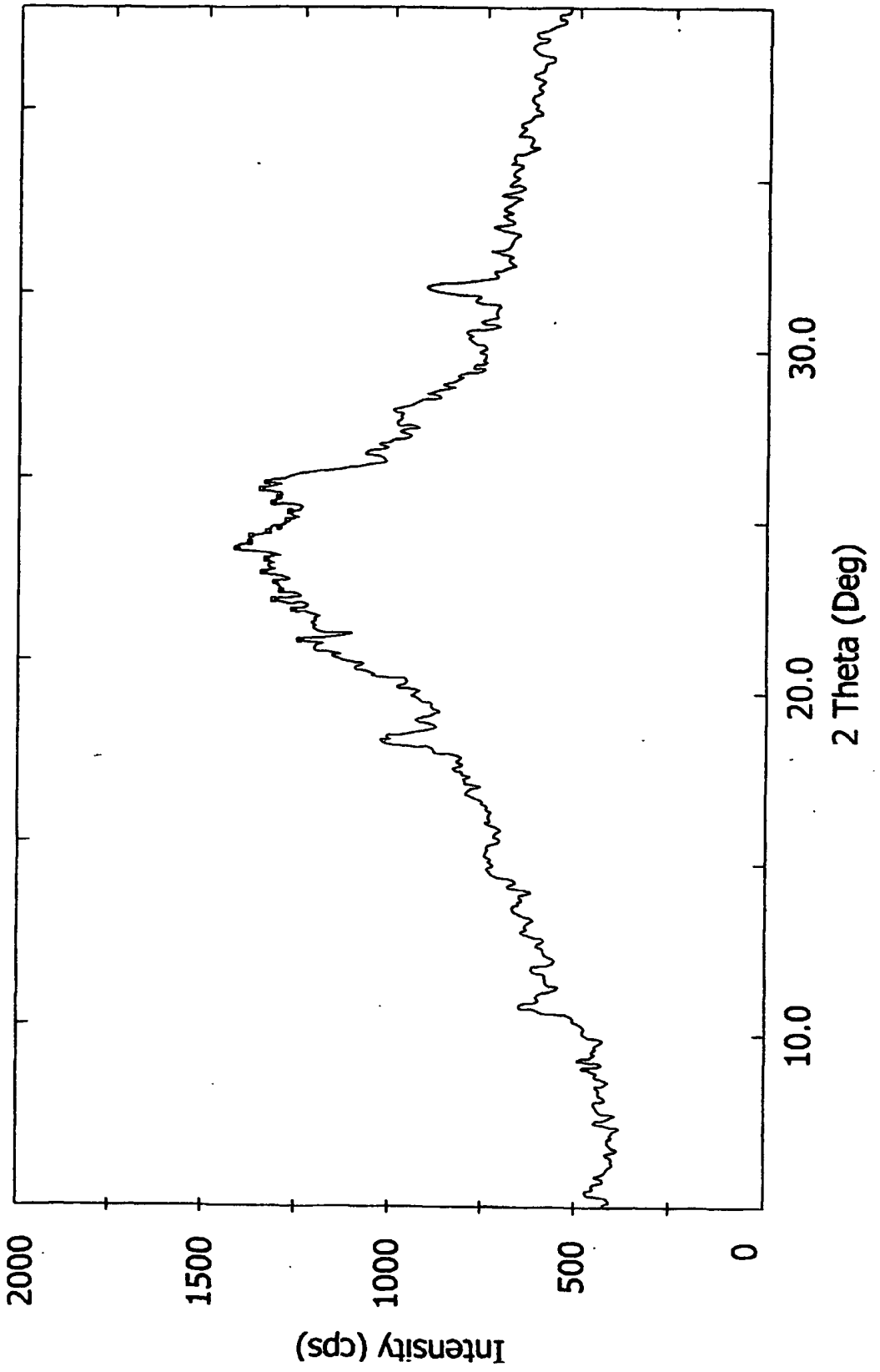

Figure 8

INTERNATIONAL SEARCH REPORT

PCT/IB04/02171

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 501/22; C07D 501/04
US CL : 540/222
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 540/222

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6093814 (Lee et al.) 25 July 2000 (25.07.2000) See abstract.	1-11, 14-18
A	US 6350869 B1 (Sturm at al.) 26 February 2002 (26.02.2002) See abstract.	1-11, 14-18
A	US 6294668 B1 25 September 2001 (25.09.2001) See examples A23-A36.	1-11, 14-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
26 July 2005 (26.07.2005)

Date of mailing of the international search report
09 AUG 2005

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Mark L. Berch
Telephone No (571)272-1600

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

PCT/IB04/02171

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-18

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB04/02171

Continuation of Item 4 of the first sheet:
Title too long. New title:

Cefdinir polymorphic forms, and imidazole salt

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-18, drawn to Imidazole adduct.

Group II, claim(s) 19-45, drawn to Forms of cefdinir and synthesis thereof.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I has the special technical feature of the imidazole adduct. This is not seen in the forms of cefdinir itself e.g. claim 19.